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Published in:
Leukemia Research

DOI:
10.1016/j.leukres.2016.09.005

Publication date:
2016

Leukemia Research 50 (2016) 37–45

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Cost-effectiveness of obinutuzumab for chronic lymphocytic leukaemia in The Netherlands

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ARTICLE INFO

Article history:
Received 20 May 2016
Received in revised form 2 August 2016
Accepted 1 September 2016
Available online 3 September 2016

Keywords:
Chronic lymphocytic leukaemia
Obinutuzumab
Chlorambucil
Rituximab
Ofatumumab
Cost-effectiveness
Costs

ABSTRACT

Background: Obinutuzumab combined with chlorambucil (GClb) has shown to be superior to rituximab combined with chlorambucil (RClb) and chlorambucil (Clb) in newly diagnosed patients with chronic lymphocytic leukaemia (CLL). This study evaluates the cost-effectiveness per life-year and quality-adjusted life-year (QALY) of GClb compared to RClb, Clb, and ofatumumab plus chlorambucil (OClb) in The Netherlands.
Methods: A Markov model was developed to assess the cost-effectiveness of GClb, RClb, Clb and other treatments in the United Kingdom. A country adaptation was made to estimate the cost-effectiveness of these therapies in The Netherlands using Dutch unit costs and Dutch data sources for background mortality and post-progression survival.
Results: An incremental gain of 1.06 and 0.64 QALYs was estimated for GClb compared to Clb and RClb respectively, at additional costs of €23,208 and €7254 per patient. Corresponding incremental cost-effectiveness ratios (ICERs) were €21,823 and €11,344 per QALY. Indirect treatment comparisons showed an incremental gain varying from 0.44 to 0.77 QALYs for GClb compared to OClb and additional costs varying from €7041 to €5028 per patient. The ICER varied from €6556 to €16,180 per QALY. Sensitivity analyses showed the robustness of the results.
Conclusion: GClb appeared to be a cost-effective treatment strategy compared to RClb, OClb and Clb.

1. Introduction

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia occurring in the Western world [1]. The age standardised incidence rate in the Netherlands is 3.8 per 100,000 [2]. Five-year relative overall survival (OS) increased from 61% in 1989–1993 to 70% in 2004–2008 for males, and for females from 71% to 76%. The majority of the patients diagnosed with CLL are above 65 years and have comorbidities.

A wait and see approach is common for Dutch patients diagnosed with CLL [3]. However, eventually many patients receive treatment. Currently, in the Netherlands, fludarabine, cyclophosphamide and rituximab is the recommended regimen for fit patients, i.e. patients without comorbidities, usually younger than 65–70 years. Chlorambucil plus a monoclonal antibody is recommended for less fit patients, i.e. patients with some comorbidities and/or WHO performance status 0–2. For unfit patients, i.e patients with several comorbidities and/or WHO performance status 3–4, chlorambucil or chlorambucil plus a monoclonal antibody is recommended [4]. There are several monoclonal antibodies available for newly diagnosed patients with CLL such as rituximab, obinutuzumab and ofatumumab. The efficacy of these therapies was investigated in randomised phase III studies, i.e. the CLL11 [5] and COMPLEMENT 1 [6]. The CLL11 study was a three arm phase III

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; ITC, indirect treatment comparison.

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http://dx.doi.org/10.1016/j.leukres.2016.09.005

study that compared both obinutuzumab combined with chlorambucil (GClb) and rituximab combined with chlorambucil (RClb) to chlorambucil (Clb) in newly diagnosed patients with CLL who required treatment. Median PFS was 26.7, 16.3 and 11.1 months for GClb, RClb and Clb, respectively [5]. The COMPLEMENT 1 study compared ofatumumab combined with chlorambucil (OClb) to Clb, and showed a median PFS of 22.4 and 13.1 months, respectively [6]. While a direct comparison between GClb and OClb is not available, it is possible to perform an indirect comparison since both the CLL11 and COMPLEMENT 1 trial included Clb as comparative treatment.

A comprehensive cost study among patients with CLL in the Netherlands showed that costs varied considerably between treatments, with Clb having the lowest total monthly costs [7]. The cost-effectiveness of GClb compared to RClb, OClb and Clb in the United Kingdom (UK) was calculated by Becker et al. [8]. However, these results might not be applicable to the Dutch context. First, input parameters such as drug prices and costs related to supportive care may not be similar. Second, guidelines for conducting economic evaluations in the Netherlands are different from the guidelines in the UK. For example, discount rates for effects and costs are different [9,10]. Therefore, we aim to evaluate the cost-effectiveness of GClb compared to RClb, OClb and Clb in The Netherlands using an adjusted version of the UK model [8].

2. Materials and methods

Evaluating the cost-effectiveness of treatments often requires modelling to bring together data sources and to extrapolate costs and effects over time. Modelling enables to compare all treatment options, not only the options that have been compared in a clinical study [11]. Modelling consists of several steps including creating a model structure (consisting of health states), assigning transition probabilities to each health state and selecting input parameters such as utility values and costs for each health state. Finally, sensitivity analyses are performed to examine the impact of assumptions and uncertainty across input parameters.

2.1. Model structure

A Markov model enables the study of the course of the disease by simplifying the disease course in health states. A Markov model including three mutually exclusive health states, i.e Progression Free Survival (PFS) (with/without therapy), Progression (Refractory/Relapsed lines) and Death (Fig. 1) was developed by Becker et al. to assess the cost-effectiveness of GClb, RClb, Clb and other treatment options in the UK [8]. A country adaptation to the UK model was made to estimate the cost-effectiveness of these therapies in The Netherlands from a healthcare perspective (Table 1).

2.2. Transition probabilities

Transition probabilities determine how patients move between health states in the Markov model. Transition probabilities from the PFS health state were derived from the CLL11 study. Observed Kaplan-Meier data was extrapolated using several parametric distributions (i.e. Exponential, Weibull, Log-logistic, Lognormal, Gamma and Gompertz). The goodness of fit of the distributions to the data was assessed using the Akaike Information Criterion (AIC), graphical assessment and knowledge of the expected extrapolation of PFS [8].

To compare GClb with OClb, an indirect treatment comparison (ITC) was made using a fixed-effects network meta-analysis (NMA). Besides the CLL11, the COMPLEMENT 1 trial was included in this network. Table 2 provides an overview of the patient characteristics of the patients in CLL11 and COMPLEMENT 1. In the study by Becker et al. the natural logarithms of the estimated hazard ratios were used to inform the ITC (unpublished results). In the current study, two scenarios for the ITC were created. Besides the natural logarithms of the estimated hazard ratios (Scenario A), the observed median PFS was used to inform the ITC (Scenario B). The latter analyses were performed with an adapted version of the WinBUGS code of Dias et al. [12,13]. Transition probabilities were supplemented with Dutch background mortality [14].

Transitions probabilities from the Progression (Refractory/Relapsed lines) health state were obtained from the Dutch Population based HAematological Registry for Observational Studies (PHAROS-registry) [15,16]. A population similar to the CLL11 population was selected from this registry by selecting patients with CLL (i.e. morphology code 9670 and 9823) who received first-line treatment with either Clb (N = 398) or RClb (N = 43). Since date of progression was frequently unavailable for patients in the PHAROS-registry, the start of second-line treatment was used as a proxy for all patients. Patients who did not receive a subsequent therapy after first-line therapy were excluded (N = 119), just as patients who have died during first-line therapy (N = 92). Table 2 provides an overview of the patient characteristics of the CLL11 study and the PHAROS-registry. To estimate the probability of transitioning from Progression to Death, a range of parametric survival distributions were compared. The distributions were assessed for their goodness of fit to the data using the AIC and Bayesian Information Criterion (BIC). Additionally, the parametric functions were assessed graphically. Finally, the impact of first-line treatment and prognostic factors (i.e. age, sex, Binet stage, WHO performance status and the number of comorbidities) on post progression survival (PPS) was tested. OS was significantly influenced by age and comorbidities. Prevalence of $\geq$2 comorbidities and/or age $\geq$65 years of the COMPLEMENT 1 (83%) was comparable to the PHAROS population (82%). However, the average number of comorbidities based on the cumulative illness rating scale in the CLL11 study was much higher. First-line treatment did not significantly influence OS, however, this could be related to the fact that only 10 of the 230 patients had received RClb as first-line treatment.

The PHAROS-registry has been approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam (MEC-2011-200), The Netherlands (metc@erasmusmc.nl) that serviced as the Dutch Medical Ethics committee. The ethic committee decided that informed consent was not to be sought, as is the policy for the Netherlands Cancer Registration.

2.3. Health state utilities

Utility values generally range between 0 (death) and 1 (perfect health). The time a patient spent in each health state was weighted using the utilities provided by Kosmas et al. [17]. The values are presented in Table 1 and are in line with the cost-effectiveness model published by Becker et al. [8].

2.4. Drug costs and drug administration costs

In the base case, drug costs were based on the planned dose based on average patient characteristics. Average weight and Body Surface Area were derived from the PHAROS-registry. The costs for entire vials were applied assuming no vial sharing. Obinutuzumab and ofatumumab are given in a fixed dose, and therefore do not depend on patient characteristics [5,6]. Dutch drug costs were derived from reference price lists (i.e. Z-index).

The administration costs of obinutuzumab, rituximab or ofatumumab infusion were assumed to be equal to the costs of a day care treatment, and to be in accordance with the number of cycles [5,6].

Table 1
Model input parameters of the UK model and the Dutch country adaptation.

Input parameters	UK model	Sources	Country adaptation	Sources
Transition probabilities				
From the PFS health state	CLL11 (and ITC)	Goede et al. [5]	CLL11 (and ITC)	Goede et al. [5]
From the Progression health state	CLL5 (CLL8 in sensitivity analyses)	Eichhorst et al. [19], Hallek et al. [22]	PHAROS-registry (CLL5 in sensitivity analyses)	Huijgens et al. [15]
Utilities				
PFS health state, under oral Treatment	0.71	Kosmas et al. [17]	0.71	Kosmas et al. [17]
PFS health state, under iv Treatment	0.67	Kosmas et al. [17]	0.67	Kosmas et al. [17]
PFS health state on initial therapy with increased hospital visits	0.55	Kosmas et al. [17]	0.55	Kosmas et al. [17]
PFS health state, after Treatment	0.82	Kosmas et al. [17]	0.82	Kosmas et al. [17]
Progression health state	0.60	Kosmas et al. [17]	0.60	Kosmas et al. [17]
Cost data				
Drugs				
Obinutuzumab (1000 mg)	£2,803.00	British National Formulary, October 2013	€4,139.43	Dutch reference price lists (Z-index)
Rituximab (500 mg)	£873.15	British National Formulary, October 2013	€1,378.40	Dutch reference price lists (Z-index)
Chlorambucil (per tablet)	£1.62	British National Formulary, October 2013	€1.18	Dutch reference price lists (Z-index)
Ofatumumab (1000 mg)	£1,820.00	British National Formulary, October 2013	€2,448.60	Dutch reference price lists (Z-index)
Weekly Supportive care costs				
PFS health state	£8.13	2012–2013 DH HRG (WF01A)	€70.51	Holtzer-Goor et al. [7]
Progression health state	£24.38	2012–2013 DH HRG (WF01A)	€418.44	Holtzer-Goor et al. [7]
Treatment administration				
Administration cost per treatment cycle	£343.00	2012-13 DH HRG (SB15Z)	€184.00	Gaultney et al. [23]
Adverse events				
Anaemia	£2088	2012-13 DH HRG tariffs (SA03F)	€ 1822	Bouwmans et al. [18]
Febrile neutropenia	£3894	2012-13 DH HRG tariffs (PA45Z)	€ 2853	Bouwmans et al. [18]
Infection	£773	Unknown	€ 2429	Opendisdata 2013 19999004
Infusion related reaction: bronchospasm	£359	2012-13 DH HRG tariffs (WA16Y)	€ 995	Opendisdata 2013 109699017/109699018
Infusion related reaction: chills	£359	2012-13 DH HRG tariffs (WA16Y)	€ 758	Opendisdata 2013 182199008
Infusion related reaction: dyspnoea	£359	2012-13 DH HRG tariffs (WA16Y)	€ 995	Opendisdata 2013 109699017/109699018
Infusion related reaction: hypertension	£359	2012-13 DH HRG tariffs (WA16Y)	€ 616	Opendisdata 2013 90301004
Infusion related reaction: hypotension	£359	2012-13 DH HRG tariffs (WA16Y)	€ 616	Opendisdata 2013 90301004
Infusion related reaction: pyrexia	£359	2012-13 DH HRG tariffs (WA16Y)	€ 758	Opendisdata 2013 182199008
Infusion related reaction: vomiting	£359	2012-13 DH HRG tariffs (WA16Y)	€ 758	Opendisdata 2013 182199008
Leukopenia	£942	2012-13 DH HRG tariffs (PA48B)	€ 1788	Opendisdata 2013 182199003
Lymphopenia	£942	2012-13 DH HRG tariffs (PA45Z)	€ 1788	Opendisdata 2013 182199003
Neutropenia	£3894	2012-13 DH HRG tariffs (PA45Z)	€ 1299	Opendisdata 2013 182199003
Pneumonia	£1353	2012-13 DH HRG tariffs (DZ11C)	€ 1593	Opendisdata 2013 109999003/109999064
Rash maculo-papular	£500	2012-13 DH HRG tariffs (PA66Z)	€ 758	Opendisdata 2013 182199008
Thrombocytopenia	£1847	2012-13 DH HRG tariffs (SA12F)	€ 3424	Bouwmans et al. [18]
Background mortality	Data representing the 2008–2012 UK population – Total population		Data representing the 2013 NL population	Statistics Netherlands [14]
Discount rates for outcome and costs	3.5% and 3.5%		4.0% and 1.5%	

Abbreviations: DH HRGs, Department of Health Healthcare Resource Groups.

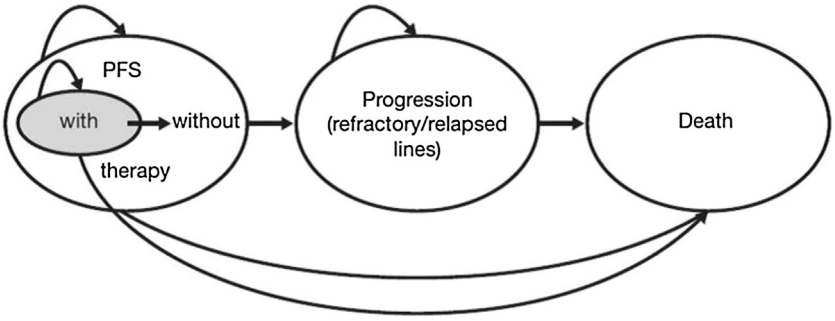

Fig. 1. Markov model structure (obtained from Becker et al. [8]).
The model includes three mutually exclusive health states: 'progression-free survival (PFS) (with/without therapy)', 'progression (refractory/relapsed lines)' and 'death'. All patients start off in the initial treatment health state and can move to another health state or stay in the same state at the end of each subsequent analysis cycle. The possible transitions are indicated by the arrows [5].

Table 2
Patient and disease characteristics of the CLL11, Complement1 and PHAROS registry.

	CLL11 GClb	CLL11 RClb	CLL11 Clb	COMPLEMENT 1 OClb	COMPLEMENT 1 Clb	PHAROS registry RCLB or CLB
Characteristics	333	330	118	221	226	230
Age, yr., median (range)	74 (39–89)	73 (40–90)	72 (43–87)	70 (36–91)	69 (35–92)	70 (39–95)
Sex male, n (%)	203 (61%)	204 (62%)	75 (64%)	142 (64%)	140 (62%)	145 (63%)
ECOG/WHO PS, median	1	1	1			
0,1 n(%)				205 (91%)	204 (92%)	150 (97%)
2 n(%)				19 (8%)	17 (8%)	3 (2%)
3–5 n(%)				0	0	1 (1%)
Unknown, n						76
Binet stage, n(%)						
A	74 (22%)	72 (22%)	24 (20%)	70 (31%)	77 (35%)	101 (44%)
B	142 (43%)	135 (41%)	50 (42%)	87 (38%)	74 (33%)	53 (23%)
C	117 (35%)	121 (37%)	44 (37%)	69 (31%)	70 (32%)	76 (33%)
Unmutaed IGHV, %	62%	61%	58%	57%	56%	N/A
FISH cytogenetics						not tested/unknown in 79% of the patients
17p-, n (%)	22 (7%)	20 (7%)	10 (10%)	10 (5%)	17 (8%)	
11q-, n (%)	47 (16%)	50 (17%)	14 (14%)	40 (19%)	24 (11%)	
12+, n (%)	46 (16%)	47 (16%)	16 (16%)	35 (17%)	34 (16%)	
13q-, n (%)	85 (29%)	46 (16%)	32 (33%)	122 (58%)	105 (49%)	
Other, n (%)	21 (7%)	85 (29%)	10 (10%)			
Normal, n (%)	74 (25%)	21 (7%)	15 (15%)	41 (26%)	64 (37%)	
6q-, n (%)				2 (<1%)	4 (2%)	
β2-microglobulin, n(%)						
<3.5 mg/l	208 (64%)	195 (61%)	70 (61%)	48 (22%)	61 (29%)	N/A
≥3.5 mg/l	115 (36%)	127 (39%)	45 (39%)	169 (78%)	153 (71%)	N/A
Total CIRS score, median (range)	8 (0–22)	8 (0–18)	8 (0–18)	8 (4–19)	9 (4–21)	N/A

Abbreviations: ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organisation; PS, performance status; FISH: Fluorescence in situ hybridization; CIRS, Cumulative Illness Rating Scale.

The occurrence of adverse events was obtained from the CLL11 and COMPLEMENT 1 trials. According to the CLL11 study, adverse events (grade ≥3) occurred more frequently among patients treated with GClb (70%) and RClb (55%) compared to Clb (50%) [5]. The COMPLEMENT 1 trial revealed that 50% of the patients treated with OClb and 43% of the patients treated with Clb experienced an adverse event (grade ≥3) [5,6]. Unit costs for anaemia (grade 3), febrile neutropenia (grade 3 and 4), neutropenia (grade 3 and 4) and thrombocytopenia (grade 3 and 4) were derived from the Dutch cost study by Bouwmans et al. [18]. The remaining unit costs for adverse events were obtained from a public database including data on average prices paid for health care products provided in Dutch hospitals (www.opendisdata.nl). Since health care products were not available for adverse events directly, the most appropriate health care product was identified based on expert opinion.

2.5. Supportive care costs

Costs of supportive care during PFS were derived from a study by Holtzer-Goor et al. [7]. In this study on real-world costs of CLL in The Netherlands, total monthly costs per treatment group are presented. Costs of chemo(immuno-) therapy and hospitalisations due to other reasons were excluded in order to prevent double counting in the model. We assumed that the total monthly costs of patients treated with Clb (N = 96) best represent the total monthly costs of patients treated with either GClb, RClb, OClb and Clb only.

Costs of supportive care during PD were also derived from the study by Holtzer-Goor et al. [7]. However, since this study included patients diagnosed between 1999 and 2003, treatment prescription might have changed. Therefore, the PHAROS-registry was used to provide more recent information on treatment prescription; costs derived from Holtzer-Goor were weighted using the distribution of treatments prescribed in second and subsequent lines as observed in the PHAROS-registry (Appendix A).

2.6. Sensitivity analyses

Deterministic sensitivity analyses were conducted to examine the impact of alternative input parameters on the incremental cost-effectiveness ratio (ICER). The amount of drugs (without or with

Table 3
Base-case: Mean costs and effects of GClb, RClb and Clb.

Effects	Mean			Incremental		
	GClb	RClb	Clb[a]	GClb vs. Clb	RClb vs. Clb	GClb vs. RClb
Years in PFS	2.75	1.58	0.99	1.76	0.59	1.17
Years in PD	3.70	4.23	4.29	−0.59	−0.06	−0.53
Total LYs	6.45	5.81	5.28	1.17	0.53	0.64
QALYs in PFS	2.19	1.23	0.78	1.41	0.46	0.96
QALYs in PD	2.20	2.52	2.55	−0.35	−0.03	−0.32
Total QALYs	4.39	3.75	3.33	1.06	0.42	0.64
Costs						
Total PFS costs	41,503	22,350	4377	37,125	17,973	19,152
Obinutuzumab	28,608	0	0	28,608	0	28,608
Rituximab	0	14,571	0	0	14,571	−14,571
Chlorambucil	195	230	209	−14	21	−35
Ofatumumab	0	0	0	0	0	0
Drug administration	1455	1027	0	1455	1027	427
Supportive care PFS	9781	5737	3634	6147	2103	4044
Adverse events	1464	784	534	930	250	680
Total PD costs	69,467	81,366	83,384	−13,918	−2019	−11,899
Total costs	110,969	103,716	87,762	23,208	15,954	7254
Costs per LY				19,810	29,967	11,350
Costs per QALY				21,823	37,624	11,344

[a] Treatment with Clb was only included in the randomisation during the first stage of the CLL11.

Table 4
Indirect treatment comparison – Mean costs and effects of GClb and OClb.

Effects	Scenario A			Scenario B		
	Mean		Incremental	Mean		Incremental
	GClb	OClb	GClb vs. OClb	GClb	OClb	GClb vs. OClb
Years in PFS	2.75	1.40	1.35	2.75	1.91	0.84
Years in PD	3.70	4.28	−0.58	3.70	4.13	−0.43
Total LYs	6.45	5.68	0.77	6.45	6.05	0.41
QALYs in PFS	2.19	1.08	1.11	2.19	1.50	0.69
QALYs in PD	2.20	2.55	−0.35	2.20	2.46	−0.26
Total QALYs	4.39	3.62	0.77	4.39	3.96	0.44
Costs						
Total PFS costs	41,503	23,324	18,178	41,503	25,136	16,367
Obinutuzumab	28,608	0	28,608	28,608	0	28,608
Rituximab	0	0	0	0	0	0
Chlorambucil	195	530	−335	195	530	−335
Ofatumumab	0	16,063	−16,063	0	16,063	−16,063
Drug administration	1455	1276	179	1455	1276	179
Supportive care PFS	9781	5093	4688	9781	6904	2877
Adverse events	1464	363	1102	1464	363	1102
Total PD costs	69,467	82,617	−13,150	69,467	78,792	−9326
Total costs	110,969	105,941	5028	110,969	103,928	7041
Costs per LY			6532			17,364
Costs per QALY			6556			16,180

vial sharing and actual dose or planned dose), treatment duration (actual or according to label) and post progression mortality rate (age adjusted pooled post progression death rate from the PHAROS-registry or age adjusted pooled post progression death rate from CLL5 trial [19] as used by Becker et al. [8]) were varied.

Probabilistic sensitivity analysis (PSA) was performed to explore the joint uncertainty across all input parameters. In the PSA, probability distributions for input parameters were used instead of point estimates to reflect the uncertainty of these parameters. Input parameters were varied simultaneously and the model was run 10,000 times. The following input parameters were varied in the probabilistic sensitivity analysis (PSA); utilities, the HR derived from the ITC, parameters for the parametric PFS and PPS function, both the occurrence and costs of adverse events, weekly supportive care costs and administration costs.

3. Results

Model results showed that GClb was the most effective treatment strategy, life-years (LYs) were 6.45 while QALYs were 4.39 (Table 3). Treatment with RClb resulted in 5.81 LYs and 3.75 QALYs. LYs and QALYs for Clb were 5.28 and 3.33, respectively. An incremental gain of 1.17 and 0.64 LYs was estimated for GClb compared to Clb and RClb respectively, at an additional cost of €23,208 and €7254 per patient. The resulting ICERs were €19,810 and €11,350 per LY, respectively. An incremental gain of 1.06 and 0.64 QALYs was estimated for GCLb compared to Clb and RClb respectively. The corresponding ICERs were €21,823 and €11,344 per QALY.

The ITC for GCLb compared to OClb showed an incremental gain of 0.77 LYs and 0.77 QALYs for scenario A (Table 4). Additional costs were €5028 resulting in an ICER of €6532 per LY and €6556 per QALY. For Scenario B, the ITC for GCLb compared to OClb showed

Table 5
Results of the deterministic sensitivity analyses.

		Costs per QALY				
		GClb vs. Clb	RClb vs. Clb	GClb vs. RClb	GClb vs. OClb (scenario A)	GClb vs. OClb (scenario B)
	Base case	21,823	37,624	11,344	6556	16,180
	Sensitivity					
Utilities						
PFS health state, under oral	0.64	21,314	35,500	11,344	6556	16,180
treatment (±10%)	0.78	22,356	40,018	11,344	6556	16,180
PFS health state, under iv	0.60	22,271	40,352	11,217	6460	15,766
treatment (±10%)	0.74	21,391	35,241	11,474	6655	16,617
Progression free survival on initial therapy	0.50	21,909	37,624	11,419	6592	16,338
with fjjjincreased hospital visits (±10%)	0.61	21,737	37,624	11,270	6520	16,026
PFS health state, after treatment	0.74	25,161	41,802	13,415	7755	19,639
(±10%)	0.90	19,266	34,205	9827	5678	13,757
Progression health state (±10%)	0.54	21,127	37,335	10,808	6273	15,272
	0.66	22,565	37,917	11,936	6866	17,203
Drug costs						
Vial sharing	With vial sharing	21,823	34,842	13,188	6556	16,180
Amount of drug	Planned dose	21,838	37,641	11,358	6579	16,220
Amount of drug	Planned individual dose	21,839	37,093	11,723	6596	16,250
Treatment duration	According to label[a]	25,932	39,088	17,046	−2403	−4221
Supportive care costs						
Progression-free state (±25%)	€ 53	20,378	36,384	9763	5028	14,527
	€ 88	23,267	38,864	12,925	8084	17,833
Progression state (±25%)	€ 314	25,094	38,814	15,996	10,843	21,537
	€ 523	18,551	36,434	6692	2270	10,823
Post progression mortality rate	Age adjusted pooled post progression death rate from CLL5 trial	22,659	37,445	13,366	8934	18,131

[a] For ofatumumab, only limited information was available on "treatment duration according to label". This deterministic sensitivity analysis assumes 12 cycles (for patients in the PFS health state).

an incremental gain of 0.41 LYs and 0.44 QALYs. Incremental costs were €7041 and the ICER was €17,364 and €16,180 per LY and QALY, respectively.

In all comparisons, the main cost drivers for the incremental costs are the drug costs of either obinutuzumab, rituximab or ofatumumab, and the costs of supportive care during progressive disease.

The results of the deterministic sensitivity analyses are presented in Table 5. The ICERs, specifically those derived from the ITC, are sensitive to the utility assigned to the PFS health state (after treatment), treatment duration, i.e. whether the actual treatment duration or the treatment duration according to the label was implemented in the model, supportive care costs and post-progression mortality rate. ICERs are slightly influenced by the amount of drugs, i.e. without or with vial sharing and actual dose or planned dose. Also the post progression mortality rate had little influence on the ICERs.

The uncertainty around the total costs and QALYs as obtained from the probabilistic sensitivity analysis is shown by Fig. 2A and B. Fig. 2A shows the comparison of GClb vs. Clb, RClb vs. Clb and GClb vs. RClb. This figure shows that GClb and RClb are more effective than Clb in 100% of the simulations. Compared to RClb, GClb is also more effective in 100% of the simulations.

Fig. 2B shows the results from the PSA for GClb compared to OClb for scenario A and scenario B. GClb is more effective in 100% of the simulations in both scenario A and scenario B, and more costly in 65% and 71% of the simulations for scenario A and scenario B, respectively.

4. Discussion

This study evaluated the cost-effectiveness of GClb compared to RClb, OClb and Clb in The Netherlands. While ICERs for the UK were available, this study managed to calculate ICERs that are applicable to the Dutch health care setting by using Dutch input parameters. Furthermore, the RCT data was supplemented with real-world post-progression data to improve the generalisability of the results. While there is no official threshold in the Netherlands, the National Health Care Institute has defined categories of maximum additional costs per QALY depending on disease burden [20]. GClb is a cost-effective treatment option in the Netherlands for previously untreated patients with CLL and coexisting conditions given that the ICERs are below €50,000 per QALY (i.e. the willingness to pay for the category with a disease burden between 0.41 and 0.7 [21]). The ICER of GClb vs Clb was €19,810 per LY and €21,823 per QALY, and the ICER of GClb vs RClb was €11,350 per LY and €11,344 per QALY. In addition, the ITC showed that the ICER of GClb was favourable compared to OClb; the ICER ranged from €6532 to €17,364 per LY and €6556 to €16,180 per QALY. The sensitivity analyses showed the robustness of the results.

Since a direct comparison between GClb and OClb was not available, an indirect comparison was performed. This ITC has some limitations; first, only two trials were included and therefore it was not possible to account for heterogeneity between trials. Second, assumptions underlying the ITC were violated; the ITC assumes that the survival curves for the common comparator (i.e. CLB) are comparable. Although the inclusion criteria of the CLL11 and COMPLEMENT 1 study were rather similar, patients in the COMPLEMENT 1 were slightly younger and had more often a Binet stage A. In addition, the dosing of Clb was different in the two trials. As a consequence, the median PFS of patients treated with Clb differed, i.e. 11.1 months in the CLL11 and 13.1 months in the COMPLEMENT 1 study. Potentially, the incremental effect of the intervention (i.e. GClb) could be larger if the comparative treatment is less effective. Furthermore, the ITC assumes that the proportional hazard assumption is not violated, while it seemed that the proportional

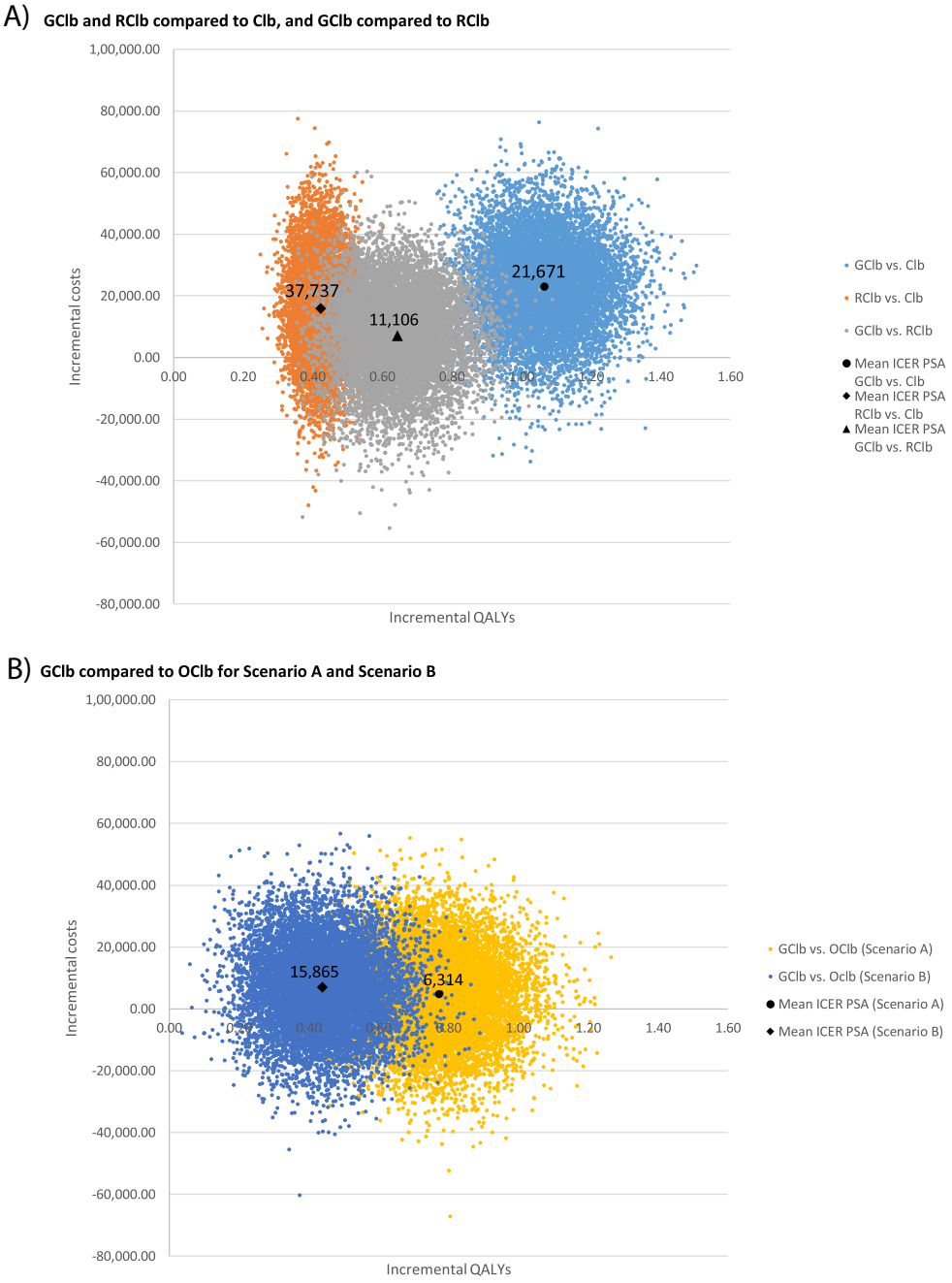

Fig. 2. Results of the probabilistic sensitivity analyses.
(A) GClb and RClb compared to Clb, and GClb compared to RClb.
(B) GClb compared to OClb for Scenario A and Scenario B.

hazard assumption does not hold over the full period. To overcome these limitations, a second scenario (Scenario B) was implemented using the median PFS to inform the ITC. Although this method does not overcome all limitations, we were able to provide a minimum and maximum ICER. Nevertheless, the ICER of GClb compared to OClb should be interpreted with caution and remains subject for further research.

PFS for all treatments was obtained from RCT data. Although RCTs are the golden standard for establishing efficacy, effectiveness in daily practice is influenced by many factors including patient characteristics and the context of health care delivery. Therefore, questions may arise to what extent the efficacy from the trial is generalisible to patients treated in daily practice. Although this is subject for further research, the generalisability regarding coexisting conditions was ensured since the CLL11 and COMPLEMENT 1 trial focused on this patient population. Furthermore, post progression survival (PPS) was obtained from real-world data, i.e. the PHAROS-registry. Ideally, PPS from the PHAROS-registry would have been calculated from the date of progression to match the model structure. However, the date of progression could not be retrieved from the registry and the start of second-line treatment was used instead. As a consequence, post progression survival was based on patients receiving second-line treatment and does not include untreated patients who progressed after first-line treatment. While using start of second-line treatment instead of progression probably underestimates PPS, excluding patients who

have died before a second-line could have started may overestimate PPS.

Supportive care costs were derived from a Dutch study by Holtzer-Goor et al. [7], and were easily applicable to the health states in the Markov model. Inclusion criteria for the study by Holtzer-Goor et al. and the CLL11 trial were a little different. All patients with CLL (except those suffering from another active malignant disease or another serious previous malignancy) were included in the study by Holtzer-Goor et al., whereas the CLL11 trial was conducted in patients with coexisting conditions. Patients in the study by Holtzer-Goor et al. were younger, and more often had a Binet stage A compared to the patients in the CLL11 study. Therefore, supportive care costs (both during PFS and PD) might have been underestimated. While this influences all treatment strategies, the potential underestimation of supportive care costs during PFS is more pronounced in treatment strategies with longer PFS (e.g. GClb) while the underestimation of supportive care costs during PD is more pronounced in treatment strategies with longer PD (e.g. Clb). Furthermore, total costs during PD might have been overestimated due to extrapolation of weekly supportive care costs in the model. Weekly costs were derived from the study by Holtzer-Goor based on a mean follow-up period of 6.4 years. However, in the model the weekly costs were applied until death. Finally, the distribution of treatments in the cost study of Holtzer-Goor et al. was adjusted to recently observed treatment patterns to calculate the costs of supportive care during PD; this assumes that the costs per treatment strategy will not change over the years and will still be representative.

Direct costs outside the health care system (including e.g. travelling expenses) were not taken into account just as indirect costs outside the health care system, such as costs associated to work days lost. Including travelling expenses was expected not to influence results since the costs associated to travelling to the hospital are very small compared to other costs such as drug costs or supportive care costs. Since the median age of the population in the CLL11 study was 73 years, we expected productivity costs also to be negligible.

Preferably, utility values should have been obtained from Dutch patients with CLL using the EQ-5D. However, since these are unavailable, utility values were obtained from a vignette study by Kosmas et al. [17]. One of the disadvantages of vignette studies is that people have their own interpretation of the health descriptions. For example, the health state *further progression* was valued with a higher utility value than *PFS on second line therapy*. Nevertheless, the limitations of the vignette study influence all treatment strategies.

Several differences exist between the base case results of the current study and the study by Becker et al. [8]. Total LYs and QALYs are higher in the current study. For example, LYs for GClb were 6.45 in the current study while LYs for GClb were 5.64 according to Becker et al. First, PFS is slightly higher in the current study due to a different discount rate for effects in the UK (3.5%) and The Netherlands (1.5%). Second, LYs in PD are substantially higher in the current study because post-progression was obtained from the PHAROS-registry. Nevertheless, post-progression was included in the deterministic sensitivity analyses (based on the CLL5 study as used by Becker et al. This revealed that although total LYs are influenced by this assumption, the impact on the ICER is small. In addition to differences for effects, total costs were much higher in the current study. For example, total costs for GClb were £34,375 (€47,916) according to Becker et al., while total costs for GClb in the current study were €110,969. This difference is caused by differences in monthly post-progression costs. In the current study, these costs were obtained from an observational study of Holtzer et al. and resulted in total progressive disease costs for GClb of €69,467. Becker et al. estimated total post-progression costs (according to the label and treatment protocol) for GClb to be £3765 (€5248).

5. Conclusions

Although this cost-effectiveness analysis has its limitations, GClb currently appeared to be a cost-effective treatment strategy compared to RClb, OClb and Clb. Results of this study can be used to inform clinical guidelines and reimbursement decisions in The Netherlands, and help to choose the optimal treatment. Nevertheless, a direct comparison should be made to supplement the current evidence for GClb compared to OClb.

Disclosures

This study was financially supported by Roche (F. Hoffmann-La Roche LTD). R de Vries and AFM van Abeelen are employed at Roche (F. Hoffmann-La Roche LTD). The remaining authors have nothing to disclose.

Contributions

HB and SdG designed the study, analysed and interpreted the data and wrote the manuscript. MA contributed to acquisition of data and data analysis. PV contributed to the design of the study and data analysis, specifically related to the indirect treatment comparison. MA, PV, RdV, AvB, EP and CU contributed to the interpretation of the data, critically revised the manuscript and approved the final version for submission.

Acknowledgements

PHAROS, the Population-based HAematological Registry for Observational Studies is a cooperation of HOVON (Dutch-Belgian Cooperative Trial Group for Hematology Oncology), the institute of Medical Technology Assessment at Erasmus University Rotterdam and the Comprehensive Cancer Organisation, the Netherlands (IKNL). PHAROS is financially supported by ZonMW 2009–2012 (#80-82500-98-01007) and through unrestricted grants from: Bayer, Roche, Janssen, Celgene, Sanofi, MSD, Novartis, GSK, Mundipharma and BMS. The authors would like to thank the various registration teams of the Netherlands Cancer Registry for data collection.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2016.09.005.

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